COGNITIVE LOAD IN MILD TRAUMATIC BRAIN INJURY: A PUPILLOMETRIC ASSESSMENT OF MULTIPLE ATTENTIONAL PROCESSES

by

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DEDICATION

This work is dedicated to all the little girls with big dreams. Be unapologetically ambitious and fearless in your journey. Set the world on fire.

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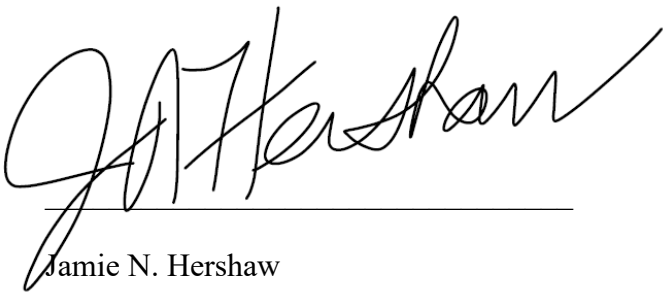

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ABSTRACT

Title of Thesis: Cognitive Load in Mild Traumatic Brain Injury: A Pupillometric Assessment of Multiple Attentional Processes

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Background and Methods: Individuals with a history of mild TBI may have an impaired ability to allocate sufficient neural resources necessary to complete cognitive tasks. Due to this reduced cognitive efficiency, cognitive tasks may impose greater demand, or cognitive load, on individuals with mild TBI compared to their uninjured counterparts. This is particulary relevant for specific attentional and executive function networks, as these networks are most vulnerable to injury, and may have behavioral consequences. Using pupillometric measures of cognitive load, the current study sought to test the effect of mild TBI on multiple attentional processes, including sustained (tonic activation), and alerting, orienting, and controlled attention (phasic activation). To test the effect of mild TBI on sustained attention, baseline pupil diameter and its variability during a sustained cued-attention task were compared between indivuduals with a remote history of mild TBI and uninjured controls. To test the effect of mild TBI on alerting,

orienting, and controlled attention, group comparisons were made for percent change in pupil diameter relative to baseline and its variability in response to various cue-target combinations designed to index each of these three processes. Finally, the relationship between cognitive load as indexed by pupillometrics and behavior was assessed for both the mild TBI group and controls. Results: The mild TBI group (n=25) had faster response time to controlled attention trials but were similar to controls (n=51) for alerting and orienting trials. Pupillometry data are mixed. They showed that the clinical sample had marginally smaller baseline pupil diameter, marginally greater baseline pupil diameter variability, and marginally greater cue-locked pupil diameter variability for controlled attention trials than controls. Moreover, a linear trend in pupil diameter variability was observed for the mild TBI group but not the control group. Finally, larger pupil diameter in response to task-relevant stimuli correlated with faster response time and less response time variability. Conclusion: Consistent with prior literature, the current study indicates that individuals with a history of mild TBI may experience greater cognitive load during controlled attention tasks. The data also suggest that those with mild TBI engage in less preparatory activation, but rather employ a reactive cognitive strategy in response to task-relevant stimuli. Moreover, this strategy is behaviorally beneficial for those with mild TBI but not uninjured controls. Additional research is warranted to substantiate claims that are based on results approaching significance.

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CHAPTER 1: Introduction

COGNITIVE LOAD

Cognitive load is the amount of demand placed onto a person's cognitive system while completing a task. The amount of mental effort and cognitive resources required to complete a task depends on cognitive load. Thus, the amount of effort and arousal levied in response to a task should be directly proportional to the cognitive load exerted by the task. Cognitive load can be measured using performance-based (e.g., response time), physiological (e.g., EEG, heart rate variability), or subjective measures (13; 74). The amount of load is dependent on both task characteristics and individual characteristics (20; 21; 30; 33). Task characteristics include features such as modality, e.g., visual or auditory stimuli, and task difficulty. Tasks that are more difficult increase the amount of load placed on an individual's cognitive system, requiring more cognitive resources to complete. Individual characteristics that increase cognitive load include variables such as age or cognitive abilities; there is great variability between individuals in the capacity and efficiency at which they can perform cognitive operations. People with neurological impairments experience greater cognitive load than their unaffected counterparts given equal task characteristics (25; 42). This effect of impairment on cognitive load is related to cognitive efficiency—the ability to minimize neural resource recruitment while maximizing performance (59). Research indicates that reduced efficiency is a consequence of impaired ability to recruit neural resources (16), which manifest as slowed reaction time and decreased accuracy (59). Although a cognitive task may be simple to perform in cognitively normal individuals, those with reduced cognitive

efficiency and limited capacity experience greater cognitive load because they do not have adequate resources to perform cognitive operations. Thus, the amount of effort they expend relative to their cognitive capacity is greater.

The behavioral and functional outcomes of cognitive operations are partly influenced by cognitive load and cognitive efficiency. In one of the earliest experiments measuring cognitive load in healthy participants, it was reported that cognitive load, modulated by task difficulty, was a significant predictor of performance decrements on a visual detection task (32). In a more recent study of healthy volunteers, task difficulty has been shown to moderate the relationship between cognitive efficiency and performance by increasing the amount of cognitive load (57). In a dual task paradigm in which the primary task greatly burdened available neural resources, participants performed worse on the secondary task relative to when the primary task required fewer neural resources. Because the more difficult primary task reduced the amount of neural resources available for the impending secondary task (i.e., increased cognitive load), the reduced cognitive efficiency for the secondary task was reflected in poorer performance. The difference in performance was most pronounced when the secondary task was also more difficult (57). These results suggest that cognitive load and cognitive efficiency interact to effect performance.

COGNITIVE LOAD IN MILD TBI

Cognitive load is higher in individuals with neurological conditions that impair cognitive efficiency, such as Schizophrenia and ADHD (27; 77). Another such condition is mild traumatic brain injury. Mild TBI is caused by a closed head injury (e.g., car accidents, falls, explosions) that results in short-duration loss of consciousness, post-

traumatic amnesia, and/or altered states of consciousness (for review of mild TBI, see (28). The principal pathophysiological sequelae of mild TBI is diffuse axonal injury (DAI) caused by axonal shearing when the head accelerates or decelerates as a result of some mechanical force (e.g., falls, collisions). DAI is known to cause abnormalities in neural network activity in a variety of brain regions, including the prefrontal cortex, via damage to white matter tracts (34; 37). Moreover, the catecholaminergic and cholinergic neurotransmitter systems are particularly vulnerable to dysregulation following head injuries (43; 44). These disrupted networks reduce cognitive efficiency associated with attentional and executive dysfunction, which are characteristic of many individuals with mild TBI (24; 64). Further, these alterations appear to be permanent; people with a remote history of mild TBI show abnormal functional recruitment many years after initial injury (4).

Because certain brain regions and neurotransmitter systems are more vulnerable to injury, some attention tasks may increase cognitive load more than other attention tasks in people with mild TBI, depending on the networks involved. Attention is often conceptualized as having three distinct networks: the alerting, orienting, and executive attention networks (18; 55; 56). The alerting network increases general cognitive arousal to facilitate fast reactions to stimuli. It is linked to activity in the right frontal and right parietal regions. Additionally, norepinephrine (a catecholamine), produced in the locus coeruleus, is a critical neurotransmitter for the alerting network. This network is considerably more diffuse than the other attention networks, likely due to its role in maintaining arousal throughout the cognitive system (17; 18; 55). The orienting network allocates resources to relevant locations or objects by enhancing perceptual processing.

This network involves the posterior parietal lobe, the superior colliculus, and the thalamus (17; 18; 55). The executive attention network is activated when the environment necessitates conflict detection and control, planning, reasoning, or inhibition of prepotent responses. The anterior cingulate cortex and lateral prefrontal cortex have been associated with this network (8; 17; 18; 55). Research has demonstrated that these three networks are structurally and functionally distinct, although there is evidence they interact (18). Moreover, it has been suggested that variations in white matter tracts may influence the efficiency of these networks (50). Mild TBI is characterized by alterations in white matter connections; accordingly, the efficiency of these networks may be impaired in mild TBI. Moreover, the efficiency of these networks may vary across networks due to the effects of mild TBI on frontal regions and cholinergic and catecholaminergic networks. Certain attention tasks which are not effortful for uninjured controls may exert greater cognitive load and require greater mental effort for people with mild TBI.

PUPILLOMETRIC ASSESSMENT OF COGNITIVE LOAD

Differences in cognitive load in individuals with a history of mild TBI may not be best indexed by performance-based measures. Evidence has shown that behavioral performance on cognitive tasks for those with TBI is often similar to that of uninjured controls, despite subjective reports of greater cognitive difficulty and neuroimaging evidence for reduced cognitive efficiency (66). Physiological measures are better able to detect changes in cognitive load than performance or subjective measures (46). One such physiological metric, pupil diameter, is sensitive and reliable for measuring fluctuations in cognitive load. It is suggested that it is the best physiological means of measuring

cognitive load because it is sensitive to within- and between-task variations and between-subjects variations (3; 68).

The pupil is innervated by the sympathetic and parasympathetic nervous systems which control the dilation and constriction of the pupil, respectively. Pupil diameter ranges in size from 1.5mm to 9mm; it can respond to stimuli as quickly as 200ms. Light and accommodation reflexes generate large fluctuations in pupil diameter to control the amount of light entering the eye. In addition to these large fluctuations in response to light, small fluctuations in pupil diameter (on the order of 0.5mm) reflect underlying cognitive operations. While these fluctuations are functionally insignificant, they can be measured to provide an index of cognitive activity. Continuous, online measurement of pupil diameter can provide information about sub-second changes in pupil diameter in response to various stimuli. Using a time-domain analysis approach, task-evoked pupillary responses (TEPRs) can be recorded. In this approach, the pupillary response is time-locked to a particular event or onset of a stimulus. Average amplitude of pupil dilation over a pre-specified time window in response to the event or stimulus onset is computed and compared to a baseline pupillary response (i.e., the average pupil diameter before the events or stimuli onset). By averaging, the signal to noise ratio of TEPR to random fluctuations in pupillary response (i.e., background noise) increases, permitting measurement of an average pupil response that is unique to specific events or stimuli.

Using this approach, a robust literature base has demonstrated that as cognitive load increases, pupil diameter increases (3; 12; 23; 31; 68; 70). The slope, peak, and duration of pupillary responses immediately following the onset of cognitive tasks are typically greater for more difficult tasks. For example, in an auditory perception task,

normal volunteers were tasked with perceiving masked speech at intelligibility levels ranging from 0% (difficult) to 99% (easy) correct. In this study, pupil diameter was largest at intermediate levels and smaller at high intelligibility levels. Interestingly, pupil diameter was smallest at the lowest, most difficult intelligibility levels, during which participants frequently reported giving up on the task. These results indicate that pupil diameter increases linearly with difficulty, until the point of cognitive overload (78). Additional research supports that the linear increase in pupillary response reverses when individuals' processing capacity is exceeded. Using a digit span task, Granholm and colleagues (1996) modulated cognitive load by having normal participants recall 5 (low load), 9 (moderate load), and 13 (excessive load) digits per string. The results indicated that pupil diameter increases with load until processing capacity is reached, at which point pupillary response plateaus; the plateau is maintained as long as participants continue to actively process the information. However, pupils begin to constrict once participants fail to allocate additional resources to the task (23). As cognitive efficiency decreases, the capacity for cognitive processing decreases. The amount of capacity utilization relative to the total processing capacity is reflected in pupil diameter such that larger pupil diameter reflects greater cognitive load on the available resources. As such, pupillometry is a useful method for quantifying resource utilization and cognitive load within an individual on a given task.

Behavioral and pupillary metrics of cognitive load are often quantified using measures of central tendency (e.g., means). An additional metric—intra-individual variability—may provide another assessment of cognitive performance within individuals. Measures of within subject variability in reaction time and pupil diameter,

including standard deviation from the mean, can quantify the consistency of behavioral responses and underlying cognitive operations. Research on variability in behavioral and ERP indices in post-concussive patients shows that individuals with a history of mild TBI have greater response time variability on a flanker task—a test of executive function—but not simpler cognitive tasks measuring lower-order cognitive processes (i.e., stimulus discrimination (53). This suggests that the effects of mild TBI on intra-individual behavioral variability may only be significant for more difficult and cognitively complex tasks. Interestingly, although average ERP amplitude was smaller in the clinical sample relative to controls, indicating reduced resource allocation, there were no group differences in intra-individual variability in ERP amplitude. Although this particular study did not find a relationship between mild TBI and variability of ERP indices of cognition, other research has demonstrated that differences in trial-to-trial neural variability are present in mild TBI (73) and may be affected by a number of variables that are relevant to mild TBI, including impaired sustained attention and arousal (7; 72) and impaired neuromodulation (40). Accordingly, intra-individual fluctuations in pupil diameter may reflect different neural responses to increased cognitive load between individuals with a history of mild TBI and uninjured controls. To our knowledge, no studies have investigated pupillary response variability as a function of cognitive load in mild TBI; however, research indicates that increased neural variability may reflect diminished integrity of underlying neurocognitive operations (10; 26; 29; 47).

PUPILLARY CHARACTERISTICS OF SPATIAL ATTENTION

Pupil diameter is closely linked to the locus coeruleus norepinephrine (LC-NE) system. The LC is located in the rostral pons and has NE projections to nearly every

region of the brain. These projections are particularly integral to attentional processes because it projects to areas such as the prefrontal cortex, parietal cortex, thalamus, and superior colliculus. Additionally, NE has an inhibitory effect on the parasympathetic nervous system; when NE is released, constriction of the pupils is inhibited, thereby permitting greater dilation under control of the sympathetic nervous system. The LC operates in two modes: tonic and phasic (1). The tonic mode is characterized by an elevated baseline firing rate and fluctuates on the order of minutes to hours. It is involved with sustaining attention and arousal. Conversely, the phasic mode is characterized by rapid firing superimposed on tonic activity in response to task-relevant stimuli. It is often measured following cues preceding the onset of target stimuli. Fluctuations in pupil diameter are highly correlated with LC-NE activity. Studies on non-human primates have revealed that baseline pupil diameter is larger with tonic activation of the LC and smaller with phasic activation. Moreover, pupil diameter increases rapidly in response to task-relevant stimuli, which is consistent with phasic firing of LC neurons in response to stimuli (22). For these reasons, pupil diameter is often used as a surrogate measure of LC-NE attention-modulating activity. It is noteworthy, however, that the direct anatomical link between the LC-NE system and pupils is unknown.

The relationship between arousal and attention is not clear; however, it is possible that increased alertness increases attentional allocation (41; 49). It is suggested that phasic firing of the LC-NE system enhances sensory processing so that individuals can prepare to direct attention to salient stimuli in the environment (5). The LC-NE system has also been implicated in attentional control. Some theories of cognitive control (the ability to inhibit prepotent responses in favor of task-appropriate responses) suggest that

cognitive control is the product of an interaction between associative learning and arousal, as modulated by the LC-NE system. Accordingly, when conflict is detected, an arousal response is triggered in the LC-NE network (69). Research has also indicated that LC-NE activity may be reduced during more difficult tasks, which then slows the processing of the cues. For example, in a target discrimination task, processing of non-predictive cues was filtered by lower LC-NE activity, relative to a less demanding target detection task (19). The authors of the same study suggest that the phasic mode of LC-NE firing is engaged for more difficult tasks, such as target discrimination, and the tonic mode is engaged for less difficult tasks, such as target localization. In the phasic mode, there is low baseline LC-NE firing coupled with greater activity in response to task-relevant stimuli. This is reflected in pupil diameter; baseline pupil diameter is smaller, but rapidly increases in response to stimuli. In contrast, the tonic mode is characterized by higher baseline firing rates and an absence of phasic responses to stimuli. This is consistent with the idea that baseline and stimulus-locked pupil dilation are inversely related. Tonic activation is also associated with poorer performance on attention tasks. In monkey studies using simple target detection tasks, increased phasic activity was associated with lower baseline activity and better performance on the task; conversely, during the same task, increased tonic mode activity (i.e., absence of phasic responses) was associated with higher baseline activity, poorer performance, and greater distractibility (58).

SUMMARY, RATIONALE, AND AIMS

In summary, the LC-NE system is likely responsible for maintaining and modulating cognitive arousal to facilitate attentional processing. Allocation of attentional

processing resources is modulated by arousal; in order to meet the demands of a task, arousal must be increased. Thus, the LC-NE system increases arousal in response to task demands through tonic and/or phasic activity. As previously stated, cognitive load depends on task characteristics and the efficiency of cognitive resources. Thus, the amount of cognitive load imposed by a task can then be evaluated by measuring the amount of arousal that is necessary to meet those demands. In individuals with poor cognitive efficiency and less cognitive capacity, the amount of arousal (i.e., effort) required to meet task demands are likely a larger proportion of their cognitive capacity relative to normal individuals whose effort constitutes a smaller proportion of their capacity. This between-subjects difference in cognitive load should be reflected in pupil diameter.

The current study seeks to test whether a history of mild TBI influences cognitive load imposed by various attentional demands using a novel sustained attention task that engages both tonic and phasic arousal. To evoke sustained attention (tonic arousal), participants are instructed to respond continuously and frequently to visual targets. Each visual target will be preceded by a cue (phasic arousal); the cue-target combination will randomly engage either the alerting, orienting, or controlled attention networks. To test the load imposed by sustained attention modulated by tonic arousal, change in pupil response over the course of the sustained attention task will be compared between uninjured controls and individuals with a history of mild TBI. It is hypothesized that individuals with a history of mild TBI will have larger pupil diameter across the duration of the task because they will require greater arousal to sustain attention, and this baseline diameter will not vary between trial type. The mild TBI group is also hypothesized to

have more variable tonic pupillary response because it is thought to reflect impaired ability to sustain attention. Moreover, it is expected that the rate of change in pupil diameter will be greater as their cognitive efficiency is exhausted over the duration of the task. To test the cognitive load imposed by the alerting, orienting, and controlled attention trials, change in pupil diameter during each of the three trial types will be compared. Because individuals with mild TBI are more likely to have reduced cognitive efficiency in the prefrontal region and dysregulated norepinephrine systems, it is hypothesized that they will have greater cognitive load, evinced by larger pupil diameter, during alerting and controlled attention trials as these networks are closely linked to frontal and norepinephrine networks. Additionally, it is expected that intra-individual variability for response time and pupillary response will be greater in the mild TBI group, particularly during controlled attention trials because these trials require higher-order cognition which is associated with increased variability. Change in pupil diameter and pupil diameter variability over the duration of the task is expected to be greater in the mild TBI group, particularly for controlled attention trials as they are more cognitive demanding. Finally, this study will examine the relationships between tonic and phasic pupillary response and performance on the task. It is hypothesized that larger and less variable stimulus-locked pupil diameter in response to task stimuli (phasic activation) will be associated with faster and less variable task performance. Conversely, it is hypothesized that larger and more variable baseline pupil diameter over the duration of the task (tonic activation) will be associated with poorer performance.

CHAPTER 2: Methods

STUDY PARTICIPANTS

One hundred ten participants were initially recruited for participation in a parent study. Individuals were included if they had a history of mild TBI, defined as one or more injuries that resulted in a loss of consciousness (LOC) less than 30 minutes or post traumatic amnesia (PTA) less than 24 hours, or if they had no history of head injury. For this study, twelve participants were excluded for history of moderate-to-severe TBI; 4 participants with history of head injury with alteration of consciousness (AOC) only; 7 participants for other medical conditions affecting cognitive performance; 2 individuals for failing two or more measures of response validity; 5 participants for whom technical difficulties interfered with eye tracking data acquisition; 2 participants for not completing the task; and 2 participants excluded for poor pupillary data quality. After exclusion, 25 participants with a history of mild TBI and 51 healthy controls were included. All study procedures were approved by the Uniformed Services University IRB; written informed consent was obtained from all participants. Participant characteristics are presented in Table 1.

APPARATUS

Stimulus presentation was implemented using E-Prime software and presented on a 15” LCD monitor. Manual responses were recorded using a Cedrus RB-530 response pad located directly in front of the monitor. Eye tracking data were collected using an Applied Sciences Laboratory (ASL) D6 remote desktop eye tracker at a sampling rate of 120Hz. The eye tracking camera was centrally located below the stimulus monitor.

PROCEDURE AND TASK DESIGN

After giving written informed consent, participants provided basic demographic information, including age and years of education. Participants in the head injury group provided details about their head injuries, including number of injuries, time since injuries, duration of loss of consciousness and post-traumatic amnesia. All participants completed the Weschler Test of Adult Reading (71) to estimate premorbid IQ, as crystallized verbal abilities are resilient to injury (52). They also completed the Neurobehavioral Symptom Inventory (NSI; (35) to obtain a measure of post-concussive symptoms. Following questionnaire completion, participants were seated 24" from the stimulus computer and eye tracker to begin the task. Eye movements were calibrated using a 9-point calibration screen. After calibration, participants viewed an instructional video for the computerized cognitive task that included 24 practice trials. Following the video and practice trials, participants began the task.

The computerized cognitive task in this study is a cued attention paradigm (15). At the beginning of each trial, a central fixation cross was presented between 1500-2500ms, randomly. At the end of this interval, the fixation cross was replaced by a 200ms cue interval. The cue consisted of one of the following: a white diamond; a white arrow pointing up, down, left, or right; a red arrow; a blank screen; or the fixation cross persisted. Although the task contains six various cue-target combinations, for the purpose of the present analysis, only trials that were cued by a white diamond or a white arrow were included in the analysis. This ensured that luminance characteristics were equal or within an acceptable difference range across trial types and nearly eliminates visual characteristics as a possible confound. Following a 200ms duration of the cue, a white

circle appeared (i.e., “target”) 7.5° above, below, left, or right of the central cue. This combination afforded three trial conditions: a white diamond followed by a target (non-directional cue, NDC); a white arrow pointing in the impending location of the target (directional cue, DC); and a white arrow pointing in the opposite location of the impending target (misdirectional cue, MDC). The other three conditions in the task that were not included in the analysis were a red arrow pointing left or right followed by a white target circle left or right of center (in the location congruent with the arrow direction) for which participants were instructed to withhold saccadic eye movements away from center (“no-go trial”); a blank screen during the 200ms cue interval followed by a white target circle located left, right, above, or below center; and the fixation cross remaining on screen during the 200ms cue interval. For all trials, targets remained onscreen for 1500ms, after which the fixation cross reappeared and a new trial began. Participants were instructed to maintain their gaze at the center of the screen, look at the target and press a button on the manual response pad as soon as the target appeared, and then return their gaze to center (except during no-go trials). The task consisted of four blocks of 48 trials presented in pseudorandom order. Trial type was counterbalanced within each block; each trial type was presented a total of 32 times during the task. The total duration of the task was approximately 12 minutes.

DATA PROCESSING

Metrics derived from the task were manual response time,manual response time variability, and pupil diameter recorded continuously over the duration of the task. Valid manual responses were defined by a response using the response pad that occurred during the time a target was onscreen. Participants must have maintained central fixation prior to

target onset. Accurate trials were defined as trials on which participants were fixated on the central cue at the time of target onset and they subsequently fixated on the target and pressed the correct button before the end of the trial. Response time variability was computed by calculating the intra-individual standard deviation of participants' average response times.

Pupil diameter was recorded online continuously during the duration of the task. Blinks were corrected using linear interpolation. Trials that had more than 1000ms of data loss were rejected from analysis. Following interpolation, the signal was smoothed using a 10Hz low pass FIR filter. Data were segmented in "epochs" for each trial. Epochs were time-locked the onset of the cue. Baseline pupil diameter was measured as the average pupil diameter over the 200ms preceding cue onset. Average baseline pupil diameter was computed for every trial. Cue-locked pupil diameter was defined as the average percent change in pupil diameter relative to baseline during the interval between the onset of the cue and 1000ms after target onset. A negative-going deflection in the percent change reflects pupil constriction and a positive-going deflection reflects pupil dilation. Average cue-locked pupil diameter was computed for every trial. Aggregates of both the baseline pupil diameter and the cue-locked pupil diameter were computed for each trial type by averaging across trials of the same trial type. A change in baseline pupil diameter over the duration of the task was also computed within-subjects by calculating the slope of the line of best fit (least squares method) for baseline pupil diameter over trials.

DATA ANALYSIS

Response time data were submitted to 2 (group: control and mild TBI) X 3 (trial type: DC, NDC, MDC) repeated measures to test for group differences in response time and response time variability. To test group differences in tonic pupillary activity, average baseline pupil diameter during the task was computed for each trial type and submitted to a 2 (group) by 3 (trial type) repeated measures ANOVA. Additionally, to test the change in baseline diameter over the duration of the task, baseline slope over the duration of the task was computed for each participant. This variable was submitted to an independent samples t-test to test for group differences. To test whether phasic responses to cognitive load modulations imposed by alerting, orienting, and controlled attention differ between groups and/or over the duration of the task, average percent change relative to baseline for cue-locked pupil diameter were submitted to a 2 (group) by 3 (trial type) by 4 (block) repeated measures ANOVA. Because of the pseudorandom order of trial type within each block, change in cue-locked pupil diameter over the duration of the task could only be compared by aggregating the response to individual trial types by block. Planned contrasts were used to test for a linear trend over blocks and possible group differences in such a relationship. For all other factorial tests of pupillary data, planned contrasts were a-priori specified to test for a linear relationship and possible group differences in linear relationships amongst the trial types, ordered by hypothesized cognitive load (DC/orienting < NDC/alerting < MDC/controlled attention). Corrections for unequal variance were made where appropriate. Relationships between pupillary metrics and task performance were computed using Pearson correlations.

CHAPTER 2: Results

SAMPLE CHARACTERISTICS

In this sample of 76, 35 (46%) were male. The mean age was 33.97 years (SD=11.96) and the mean years of education was 16.26 (SD=2.44). The median number of years since injury in the mild TBI group was 6.91 years (*IQR*= 3.6, 22.84). Eighteen participants in the mild TBI group (72%) sustained one head injury, whereas seven (28%) sustained two or more. As depicted in Table 1, the mild TBI group did not significantly differ from the control group on age, education, ethnicity, gender, or estimated premorbid intelligence. The mild TBI group had significantly greater symptom report on the NSI than the control group, $t(74)=-2.23$, $p<.05$. Overall, the mild TBI sample were nearly twice as symptomatic as controls.

TASK PERFORMANCE

The 2x3 repeated measures ANOVA for response time revealed a main effect of trial type, $F(1.734,128.352)=129.58$, $p<.001$, partial $\eta^2=.637$. Response times were statistically different for all trial types, $p<.01$. Directional trials were fastest, followed by non-directional, and misdirectional were the slowest trials. There was not a significant main effect for group $F(1,74)=1.73$, ns. The analysis yielded a significant two-way interaction between group and trial type, $F(1.734,128.352)=4.34$, $p=.019$, partial $\eta^2=.055$. Post-hoc analyses revealed that this interaction is driven by group differences in response time on misdirectional trials. The difference between controls (M=532ms, SD=107) and mild TBI (M=483ms, SD=134) was marginally significant, $t(74)=1.724$, $p=.089$. These results are shown in Figure 1.

The 2x3 repeated measures ANOVA computed for response time variability produced a marginally significant main effect of trial type, $F(2,148)=2.842$, $p=.061$, partial $\eta^2=.037$. Response time variability for non-directional trials was less than for directional, $p<.05$. No other comparisons between trials were significant. No main effect of group, $F(1,74)=.613$, n.s., was reported. There was no significant interaction between group and trial type, $F(2,148)=.351$, n.s. These results are depicted in Figure 2.

TONIC PUPILLARY RESPONSE

A 2 (group) by 3 (trial type) repeated measures ANOVA was computed to test group differences between average baseline pupil diameter during the task. There was a main effect of trial type, $F(2,148)=6.125$, $p<.01$. This effect is driven by misdirectional trials ($M=4.876$, $SE=.142$), which had smaller diameter than directional ($M=4.905$, $SE=.141$), $p<.01$, and non-directional trials ($M=4.905$, $SE=.141$), $p<.01$. There was a marginally significant effect of mild TBI on baseline pupil diameter, $F(1,74)=3.234$, $p=.076$. The mild TBI group ($M=4.64$, $SE=4.18$) had smaller baseline pupil diameter than controls ($M=5.15$, $SE=4.83$). No interaction between group and trial type was reported, $p=.368$. Planned comparisons yielded a significant linear effect of trial type, $F(1,74)=10.883$, $p<.01$. The results of this analysis are depicted in Figure 3.

Intra-individual variability in baseline diameter was tested using a 2 (group) by 3 (trial type) repeated measures ANOVA. A significant effect of trial type was reported, $F(2,148)=7.870$, $p<.001$, partial $\eta^2=.096$. The main effect of trial type was driven by significantly greater variability in pupil diameter prior to non-directional trials ($M=0.356$, $SE=0.021$) relative to both directional ($M=0.334$, $SE=0.020$, $p<.05$) and misdirectonal trials ($M=0.321$, $SE=0.019$, $p<.001$). Variability in pupillary response did not differ

between directional and misdirectional trials, p=.128. Group differences in baseline diameter intra-individual variability trended towards significance, F(1,74)=2.797, p=.099, partial η^2=.036. Pupil response was marginally more variable in the mild TBI group (M=0.369, SE=0.032) than in uninjured controls (M=0.305, SE=0.022). There was no significant interaction between group and trial type, p=.962. Planned comparisons yielded no significant linear effects. These results are shown in Figure 4.

Slopes of the change in pupil diameter over the duration of the task were submitted to a t-test to test for group differences. The mild TBI group (M=-0.0032, SD=0.0038) did not differ from the control group (M=-0.0022, SD=0.0028) in the slope of baseline pupil diameter over the duration of the task, t(74)=1.251, n.s. Figure 5 depicts change in pupil diameter over trials.

PHASIC PUPILLARY RESPONSE

Due to the addition of more light to the visual field when the cues appear (relative to baseline), the pupillary light reflex will generate large constrictions in pupil diameter. Importantly, luminance was comparable across the trial types included in analysis. Thus, all trials will cause large reductions in pupil diameter; however, any differences in pupil diameter can be attributable to the effect of cognitive processing on pupil size. To test the differences in the cognitive response to each of the three trial types, a 2 (group) by 3 (trial type) x 4 (block) repeated measures ANOVA was performed on cue-locked pupil diameter percent change. There was a significant main effect of trial type, F(2,148)=18.35, p<.001, partial η^2=.199. Non-directional trials had the smallest change in pupil diameter (M= -0.003, SE=0.002). Average percent change in pupil diameter for non-directional trials was significantly less than for directional (M= -0.001, SE=0.002),

$p<.05$, and misdirectional trials ($M=0.003$, $SE=0.002$), $p<.001$. Misdirectional trials evoked the greatest change in pupillary response, with greater change in diameter than directional trials, $p<.001$. There was no significant group difference, $F(1,74)=.018$, n.s., nor a significant interaction between group and trial type, $F(2,148)=1.34$, n.s. No effects of block were reported, $F(3,222)=.506$, n.s., nor interactions between block and group, $F(3,222)=.989$, n.s., or between block, trial type, and group, $F(6,444)=1.72$, n.s. Post-hoc group comparisons of pupillary response for individual trial types yielded no significant group differences for any of the three trial types. Planned contrasts revealed a linear trend for trial type, $F(1,74)=15.63$, $p<.001$. No linear trends for block were observed. Results of this analysis are depicted in Figure 6. Task evoked pupillary response waveforms for the three trial types are presented in Figure 7.

Intra-individual variability in relative change in cue-locked pupillary response was submitted to a 2 (group) by 3 (trial type) by 4 (block) repeated measures ANOVA. There was no effect of group, $F(1,74)=.505$, n.s., or trial type, $F(2,148)=1.65$, n.s. There also was no interaction between group and trial type, $F(2,148)=1.551$, n.s. A significant effect of block was reported, $F(3,222)=5.68$, $p<.01$. Table 2 provides the descriptive statistics of this finding. No interactions were observed between group and block, $F(3,222)=1.25$, n.s., or between group, trial type, and block, $F(6,444)=1.36$, n.s. Post-hoc t-tests were computed to evaluate group differences in the effect of each trial type on IIV. Results indicated that group differences did not exist for directional $t(74)=.153$, n.s., or non-directional trials $t(74)=-.867$, n.s. A marginal difference was reported for misdirectional trials, $t(74)=-1.733$, $p=.087$, wherein the mild TBI group had greater variability in pupillary response. Planned contrasts revealed a linear effect of block,

$F(1,74)=12.90$, $p<.01$. Variability in cue-locked pupillary response increased linearly over the duration of the task. A marginal interaction between group and the linear trend in trial type was also observed, $F(1,74)=3.02$, $p=.087$, partial $\eta^2=.048$. The effect of trial type on variability in pupillary response to the cues was greater in the mild TBI group than in controls. These results are depicted in Figure 8.

BEHAVIORAL CORRELATES OF PUPILLARY DIAMETER

Correlations were computed to assess the relationship between pupillary response and behavioral performance on the cognitive task. Baseline pupil diameter and variability were aggregated across trial types because they theoretically should not differ. Separate correlational analyses were performed for the two groups. Tables 3 and 4 provide correlation coefficients for both groups. As depicted in the correlation tables, the significant relationships between cue-locked pupil diameter and behavioral performance were stronger in the mild TBI group than the control group, such that greater change in pupil diameter in response to task-relevant stimuli were associated with faster and less variable response times.

CHAPTER 4: Discussion

SUMMARY OF FINDINGS

The current study sought to examine the effects of mild TBI on cognitive load and how it relates to performance on an attention task. By quantifying baseline and cue-locked pupil diameter, we were able to obtain psychophysiological measures of cognitive load over the duration of a sustained attention task and in response to task-relevant stimuli. Results from this study are mixed and inconclusive. Modest evidence indicates that mild TBI may differentially affect sustained attention and that it possibly influences the variability in selective attention. However, the results should be interpreted with caution given that many of the findings approached conventional standards of significance but did not reach the threshold.

Behavioral data were analyzed to test for differences between groups in this sample (for a more thorough discussion, see (14)). As reported elsewhere by our lab (14), participants were slower to respond to misdirectional trials than for directional or non-directional trials. This finding validates our assumption that the task invokes varying levels of cognitive load, with misdirectional trials being the most cognitively burdensome. The effect of trial type on response time varied between groups. The difference in the effects was driven by the misdirectional trials, wherein trials requiring controlled attention appeared to have less of a negative effect on response time for patients with a history of mild TBI relative to controls. Variability in response time was also compared between groups. Like response time, no group differences were reported for response time variability. The lack of overall group differences in response time and

response time variability (without respect to trial type) indicates that the mild TBI group is performing overall similarly to the uninjured controls. This is consistent with prior research showing that a majority of patients with a remote history of mild TBI do not exhibit observable behavioral deficits after the typical recovery period (9). The median time since injury in our sample was over 6 years—well beyond the typical recovery period of 3 to 6 months. However, the interaction between trial type and group that is driven by misdirectional trials indicates that the neurocognitive deficits persist in some cognitive domains. The behavioral results of the current study are taken as evidence that there may be underlying neurological differences between controls and participants with a history of mild TBI that manifest as behavioral deficits, particularly with controlled attention processes.

Interestingly, misdirectional trials slowed response time for controls more than for the mild TBI group. This pattern is counterintuitive given that the mild TBI group was expected to experience more cognitive load than controls, particularly on trials requiring controlled attention. However, it is possible that the mild TBI group has greater impulsivity and therefore faster reaction times on trials requiring inhibition of a prepotent response (i.e., misdirectional trials). Although we did not measure impulsivity in our sample, prior research indicates that participants with mild TBI often experience increased impulsivity and poorer behavioral response inhibition (11) and that impulsivity includes prefrontal cortex involvement, a region that is vulnerable to damage following mild TBI (62). While we did not measure impulsivity directly, the task used in this study did include a go/no-go trial (albeit not included in the current analyses). Subsequent analysis of ratio of errors committed to correct responses on the go/no-go trials indicates

that the mild TBI group (M=2.47, SD=4.89) committed more errors than the control group (M=0.71, SD=2.07), $p<.05$. This result supports the hypothesis that the reduced effect of controlled attention on response time in mild TBI may be attributable to greater impulsivity in this clinical sample. However, as discussed later in conjunction with pupillary results, it is also possible that the mild TBI group was less affected by the invalid cueing as a consequence of insufficient cue processing.

The cognitive task used in the current study was a sustained attention task requiring participants to respond continuously to a series of cued spatial targets. The sustained attention elements of the task permitted us to analyze the baseline pupil diameter—prior to stimulus onset—over the duration of the task. The comparison of the average baseline diameter between groups yielded a marginally significant difference which does not support our hypothesis that the mild TBI group would have larger baseline pupil diameter. Our hypothesis that the mild TBI group would have greater tonic activation is based on prior research showing that people with mild TBI require greater resource allocation to complete a task and therefore experience greater cognitive load (51; 61). The data show that uninjured controls had larger baseline diameters, indicative of greater tonic activation of the LC-NE system. Our results demonstrate that the mild TBI group experienced less tonic activation while completing the sustained attention task. This unexpected finding could reflect a number of possible non-orthogonal mechanisms, including insufficient preparatory activation for the task (63), capacity overload (78), slowed cue processing (19), or deterioration of neural activation over time (3). Participants with mild TBI are known to have deficits in the dorsolateral prefrontal cortex (54; 76). The dlPFC is also integral to preparatory activation in advance of processing

cognitive demands and increased dlPFC activity has been shown to correlate with pupil diameter (60). Accordingly, it is possible that participants with a history of mild TBI have difficulty with preparatory activation to process the cues during the sustained attention task. Thus, the reduction in baseline pupil diameter observed in the clinical sample may reflect insufficient preparatory activation for attentional processing. More deficient preparatory activation and poorer processing of cues may also explain the faster response time in response to misdirectional cues among mild TBI relative to controls. If individuals with mild TBI are not processing cues sufficiently as a consequence of insufficient preparatory activation, they may experience less cognitive conflict or not fully configure a response set and thus require less inhibition of their prepotent response. In this scenario, less inhibition for a prepotent response would lead to faster reaction times. Similarly, the reduction in tonic activation could reflect capacity overload, as pupil diameter constricts as capacity is exceeded; however, similar performance to controls indicate that the mild TBI group did not reach capacity overload. Alternatively, the reduction in pupil diameter prior to onset of cues may reflect a compensatory mechanism that functions to slow attentional processing of subsequent cues (19). This possibility is non-orthogonal to the insufficient preparatory activation hypothesis, given that slowed processing may result in insufficient preparation in the 200ms interval between the onset of the cue and the onset of the target. Finally, larger pupil diameter is most commonly associated with greater resource allocation and greater cognitive load; however, some researchers suggest that pupil diameter decreases as cognitive efficiency decreases. More difficult tasks and those that require sustained attention are presumed to deteriorate cognitive efficiency by taxing the neural networks involved and causing them to

deactivate over time (3). Thus, it is also possible that this task caused greater deterioration, or "vigilance decrement," in cognitive efficiency for the mild TBI group over time. However, as shown in Figure 5, the baseline pupil diameter for the mild TBI group never exceeded that of the controls, even in the earliest trials. Additional research is warranted to further clarify the finding that the mild TBI group had smaller pupil diameter than controls.

To investigate the group differences in variance, intra-individual variation was submitted to statistical testing. The results of this analysis trended towards significance, showing that the mild TBI group had marginally higher levels of variability in baseline pupil diameter. Although it did not reach statistical significance, this pattern indicates that the tonic activation of cognitive arousal is may be more variable within individuals with a history of remote mild TBI. A difference in variability in baseline pupil diameter is consistent with prior research indicating that variability in psychophysiological responses likely indicates the presence of neural noise caused by some underlying neural disturbance (75). Damage incurred as a result of a mild TBI may directly or indirectly contribute to this inconsistency in neural activity. We propose that greater variability of baseline pupil diameter in a sustained attention task among participants with mild TBI is reflective of underlying neurological impairment. Further, due to the inconsistency in tonic activation as measured by baseline pupil diameter, we conclude that they have impaired ability to sustain general cognitive arousal while completing an attention task. However, because the results were only marginally significant, these findings should be interpreted with caution.

Regardless of group membership, participants demonstrated greater baseline pupil diameter prior to misdirectional trials and baseline pupil diameter variability prior to non-directional trials. Because these metrics are computed by averaging over the 200ms immediately *preceding* the onset of the cue, one would expect that baseline pupil diameters and their associated variabilities would not differ from each other across trial types due to the absence of task-relevant stimuli. It is possible that, despite our best efforts, the pseudorandomization of trials in this task was not sufficient enough to be perceived as truly random. However, it is important to note that while the baseline pupil diameter was *significantly* greater for misdirectional trials, the numerical difference between misdirectional trials and the other two trials was 0.03mm. Although this difference reached statistical significance, a difference of 0.03mm in pupil diameter may not be functionally meaningful. Thus, it is also possible that this effect is a Type I error.

The slope of the change in baseline pupil diameter over the course of the task did not differ between groups. Accordingly, we the data do not support the hypothesis that cognitive efficiency would decline more rapidly in the clinical sample over the duration of the task. Our hypothesis was based upon prior research indicating that participants with mild TBI have reduced cognitive efficiency and experience impaired resource allocation relative to controls. Overall, in both groups, pupil diameter decreased over time. This is consistent with research suggesting that a decrease in pupil diameter is the result of decreased cognitive efficiency over time in a sustained attention task, or a "vigilance decrement" (3). However, there is debate over whether reduced efficiency causes pupillary constriction or dilation. It is also possible that pupil diameter decreases as a function of fatigue (48). Visual inspection of Figure 5 supports this possibility. After

each block of 48 trials, participants had a brief opportunity to disengage from the task; a spike in pupil diameter is observable at the start of each new block. Regardless of the exact cause of the gradual reduction, the data indicate that there are no differences between groups in the gradual decline of pupil diameter over the course of a sustained attention task. The mechanism that affects this decline in uninjured controls appears unaffected by mild TBI.

Contrary to our hypotheses, this study did not find any group differences in the phasic pupillary response to task-relevant stimuli. We hypothesized that the mild TBI group would have greater percent change in pupil diameter (relative to baseline) on trials indexing alerting and controlled attention networks. However, no such group differences were observed. In aggregate, participants with a remote history of mild TBI do not respond to task-relevant stimuli on a sustained attention task differently from uninjured controls. Across groups, all participants had greater pupil dilation in response to misdirectional trials, followed by directional trials, and then non-directional trials. This linear relationship is consistent with prior research indicating that more difficult tasks evoke greater resource allocation (36; 67). From this we conclude that controlled attention tasks exert greater cognitive load than alerting or orienting and requires more resource allocation, independent of group membership. Additionally, the alerting task requires the least amount of resource allocation. This is likely due to the limited amount of information contained in the cue, relative to directional cues. Directional (and misdirectional) trials were cued with an arrow which contains both temporal and spatial information about the impending target. Conversely, the non-directional trials were cued by a diamond, which only provides temporal information. Although change in pupil

diameter was greater in directional trials, indicating more cognitive load, directional trials had faster response times than non-directional trials. The fact that the pupillary response was greater for directional trials relative to non-directional trials indicates that additional processing was required for those trials—in effect, responding to combined networks (orienting) requires greater cognitive resources than more singular networks (alerting). And while attentional orienting may require additional processing, the behavioral results suggest that this additional processing may be beneficial, as response time was faster for directional trials. Although the luminance of the three trial types was similar, the non-directional trials did differ from directional and mis-directional trials in visual properties. The cue for the non-directional cue was a diamond rather than an arrow. Accordingly, the visual differences may account for some of the observed differences in pupil diameter. The non-directional trials did, in fact, have greater constriction than the other trial types. Accordingly, we must also consider the possibility that the visual characteristics of the trials may influence pupil diameter. However, the slight increase in luminance for non-directional trials is within conventional guidelines.

Intra-individual variability of phasic pupillary response was computed and submitted to statistical testing to determine if variability in pupillary response to task-relevant stimuli differs between groups. While no group differences were observed, planned comparisons revealed that the effect of trial type on variability in pupillary response differed between groups. Participants with mild TBI showed a linear trend in pupil response variability as task difficulty increased. Directional trials, with spatial cues that validly predicted the impending target, evoked less variability than non-directional trials, wherein the cues provided no spatial information and thus no advantage.

Misdirectional trials, with spatial cues that invalidly predicted the target and required additional inhibitory processing, garnered the most variability in pupillary response. This linear effect was only observed in the mild TBI group; uninjured controls exhibited similar pupillary response variability across all three trial types. This pattern of results suggests that the task manipulated the amount of cognitive load imposed on individuals with mild TBI, as evinced by the amount of variability in their pupillary response to task-relevant stimuli. While the amount of cognitive load imposed by the task on uninjured controls was constant across task conditions, the amount of load increased linearly with task difficulty for those with a remote history of mild TBI. This finding is consistent with the hypothesis that individuals with a history of mild TBI experience greater cognitive load than their uninjured counterparts (42; 45). While increases in task difficulty did not affect pupil response variability in controls, increasingly difficult task demands generated increased variability among the clinical sample. These data show that individuals with mild TBI are affected more by more difficult tasks and this is reflected in the inconsistency in the neural response to stimuli. Overall, these data support the hypothesis that individuals with a history of mild TBI have cognitive efficiency and are more likely to experience greater cognitive load as tasks become more difficult.

Additionally, post-hoc group comparisons for each trial type revealed that the mild TBI group had marginally significantly greater variability for the misdirectional trials compared to uninjured controls. The load imposed on the controlled attention network by the misdirectional trials was significantly greater for those with mild TBI. Prior research has shown that phasic activity of the LC is engaged for more difficult tasks. The misdirectional trials are arguably the most difficult of the three tasks because it

requires deployment of controlled attention to inhibit a prepotent response and re-orient attention. Indeed, our data suggest that misdirectional trials require additional processing for individuals with mild TBI. However, due to the marginal significance, these results should be interpreted with caution and additional research is need to confirm or disconfirm this finding. Behaviorally, both the clinical sample and the controls also exhibited slowed reaction time for these trials relative to other trial types. While both groups had slower response time for misdirectional trials, only the mild TBI group showed differences, albeit marginal, in cognitive processing via increased variability in cue-locked pupillary response. The current data suggest that individuals with a history of mild TBI, even years after injury, may experience impaired controlled attentional processing. Prior research supports this claim; several studies have shown that networks involved in executive functions and controlled attention are impaired in injured brains, sometimes well after the typical recovery period (24; 65). These results partially support our hypothesis that some attention networks would be less efficient and incur greater cognitive load in individuals with mild TBI. Specifically, the controlled attention network appears to be most affected. Because some of these inferences are based upon results that approach clinical significance but do not pass the threshold, α=.05, additional research is warranted to substantiate these claims.

Finally, phasic pupillary responses revealed that across all participants variability in the change in pupil diameter, regardless of task condition, became greater over the duration of the task. The finding that, overall across both groups, variability increased over the duration of the task suggests that the cognitive load evoked by the sustained attention task increased over the duration of the task. This is likely due to effects of

fatigue. The absence of group differences in the change in variability over time, and specifically for misdirectional trials, does not support our hypothesis that more cognitively demanding tasks for the mild TBI group would exhaust their cognitive systems more than controls, as evidenced by increased variability. Although when averaged over the entire task, the mild TBI group had greater variability during misdirectional trials, they did not show linear decrements in variability on misdirectional trials as the task progressed. It is possible that the negative effect of sustaining attention for a long duration did not apply to misdirectional trials because the variability in pupillary response for these trials was already high for the mild TBI group. Essentially, we argue that the deleterious effects of fatigue may only apply to easier task conditions but not for conditions that are cognitively burdensome from the beginning.

In summary, tonic activation is considered to support general arousal and vigilance, whereas phasic activation supports selective attention to task-relevant stimuli (2). Mild TBI subjects showed less baseline pupillary activity (i.e., less tonic activation) than uninjured controls. They also showed greater variability in pupil dilation (i.e., phasic activation) during controlled attention trials but not alerting or orienting trials. We hypothesized that the clinical sample would have both greater tonic and phasic activation because the sustained attention task would be more burdensome on their cognitive systems compared to controls. This increased load, theoretically, would be expressed as greater pupil diameter—a proxy for increased resource allocation. However, our data reveal that participants with mild TBI do not have increased resource allocation during the baseline of the cognitive task; in effect, they were using fewer resources and had reduced tonic activation. This effect was reversed for phasic activation: phasic activation

in mild TBI was greater than in controls for the misdirectional trials and the increase in variability as a function of task difficulty was greater in the clinical sample. This pattern suggests that individuals with a history of mild TBI have altered vigilance and controlled attention networks, many years after injury. It is plausible that neural disruptions caused by injury persist well after observable outcomes normalize and these disruptions continue to reduce cognitive efficiency. This reduction in cognitive efficiency may then result in greater cognitive load when completing cognitive tasks.

The relationships between tonic and phasic pupillary response and task performance were also evaluated in this study. We predicted that greater baseline pupil diameter and its variability would be related to slower and more variable response time. However, no correlations were observed to support this hypothesis. Prior research has shown that greater variability in underlying neural mechanisms contributes to poorer performance (38; 39). The absence of a relationship between tonic pupillary response and behavioral performance may indicate that the integrity of a general arousal network in the absence of any task-relevant stimuli is not a critical contributor to behavioral outcomes. Although tonic pupillary response did not correlate with any performance metrics, in the mild TBI group greater percent change in pupil diameter in response to task-relevant stimuli was associated with faster response time and less response time variability. This is consistent with our hypothesis that greater stimulus-locked pupil diameter (increased phasic activity) would correlate with better task performance. However, this pattern was largely absent in the control group. We did not predict that the control group would have a different relationship between phasic activation and performance relative to the mild TBI group. This is contrary to previous human and animal research showing that phasic

activation of the LC is associated with better task performance (58). Thus we conclude that phasic activation is particularly beneficial to participants with a history of mild TBI in that enhanced stimulus-driven attentional processing relates to better performance, particularly faster and more consistent behavioral responses.

Finally, our study demonstrates that individuals with a history of mild TBI may have more variable psychophysiological responses during a sustained attention task. Our results indicated that the variability in tonic pupillary response—the baseline pupil diameter—is marginally greater in the clinical sample, although the mean baseline pupil diameter is smaller. Although the differences in the average pupil diameter indicate that those with mild TBI are using less cognitive resources during the sustained attention task and are plausibly engaging in less preparatory activation, the fact that they have greater variability indicates that the underlying cognitive processes for this preparatory activation are operating inconsistently. Additionally, the variability in pupillary response time-locked to trials requiring controlled attention processes indicate that individuals with mild TBI may bee most impaired in the executive function domain. These trials required inhibition of a prepotent response and re-orientation to the correct target location. This finding is consistent with previous literature examining the amount of psychophysiological variability in response to tasks demanding higher-order cognition. The observation that the mild TBI group had marginally greater variability during misdirectional trials indicates that their cognitive processing of controlled attention is impaired relative to controls. The absence of similar effects for directional or non-directional trials suggests that individuals with mild TBI do not differ from controls in their ability to consistently engage alerting or orienting networks. Interestingly, although

mild TBI effected variability in psychophysiological responses, but not means of psychophysiological responses, it was the mean of phasic pupillary response that related to behavioral performance. Although differences in variability between the two groups were significant, pupillary response variability is unrelated to behavioral outcomes. Despite that the pupillary response to task-evoked stimuli and in a pre-stimulus baseline period are more variable in individuals with mild TBI, this variability does not seem to affect performance. Taken into context, the relationships between enhanced task-relevant stimulus processing is tenuously associated with better outcomes in mild TBI, but is unrelated to performance in controls. However, the data indicate that those with a history of mild TBI do not, on average, enhance preparatory activation, but instead might rely on stimulus-locked phasic activation. This raises the possibility that increased resource allocation in response to task-relevant stimuli is a beneficial compensatory strategy in the clinical sample. This conclusion is supported by previous research on dual mechanisms of cognitive control (6). According to this theory, cognitive control can be exerted through one of two mechanisms: proactive or reactive control. Proactive control enhances attentional processing in anticipation of and preparation for task-relevant stimuli. It requires greater cognitive resources. On the contrary, reactive control enhances attentional processing in immediate response to task-relevant stimuli. It requires less cognitive resources than proactive control (6). Trends in our data indicate that patients with a history of mild TBI may utilize a reactive control mechanism rather than proactive, possibly because of limited cognitive capacity. It is possible that a reactive strategy becomes the dominant and most successful strategy following injury because it requires less cognitive resources and is less effortful.

CONCLUSION

The current study demonstrates that individuals with a history of mild TBI experience greater cognitive load with increasing task demands relative to uninjured controls. Specifically, task conditions requiring controlled attention are particularly affected by mild TBI. This result is aligned with neuropsychological, behavioral, and neurological evidence that patients with a history of mild TBI have impaired executive functioning. The data also provide evidence that, despite unimpaired performance, individuals with remote mild TBI still experience cognitive difficulties, particularly with controlled attention/executive function. This finding is critical to the understanding of cognitive outcomes in mild TBI years after injury. Our study also shows that individuals with a history of mild TBI require greater resource allocation in response to task-relevant stimuli but are less adept at engaging preparatory activation in anticipation of the stimuli. However, greater engagement of reactive attentional processing appears to benefit those with mild TBI while it neither helps nor hurts controls. Finally, this study highlights the importance of using variability in psychophysiological responses as an outcome of interest. In the current study, aggregate analyses were less informative than intra-individual variability. Using an aggregate, particularly in a heterogeneous clinical sample, may conceal important psychophysiological differences. Psychophysiological variability is often an indicator of disruptions to underlying neural networks; accordingly, it should be used consistently to investigate and measure the integrity of neurocognitive functioning in neurologically impaired populations. However, possibly due to the limited power of the study, small sample size, and/or heterogeneity of the clinical sample, many of these conclusions are derived from marginally significant results;

interpretation of these results must be made cautiously and it is critical that additional research is conducted to substantiate these claims.

Figures

Figure 1: Manual Response Time

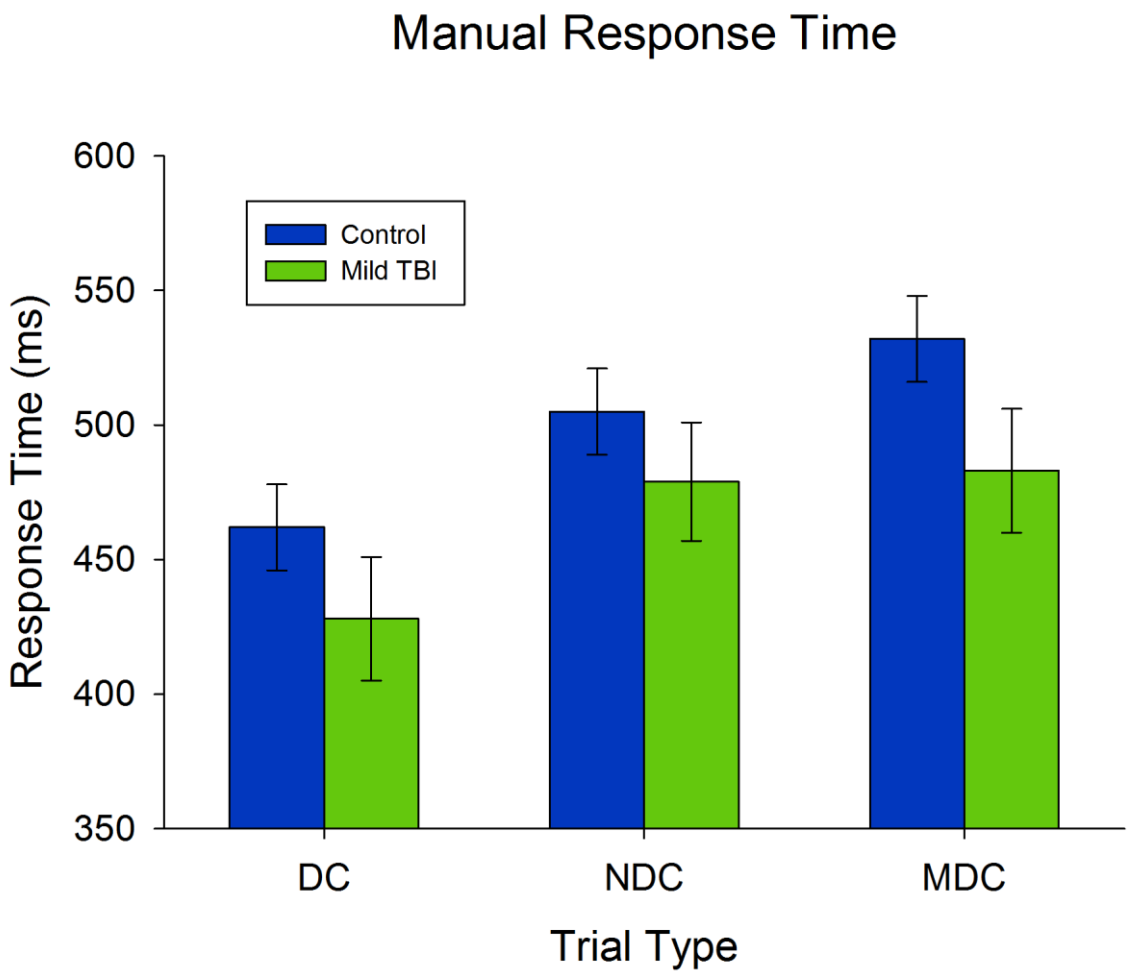


Figure 2: Manual Response Time Variability

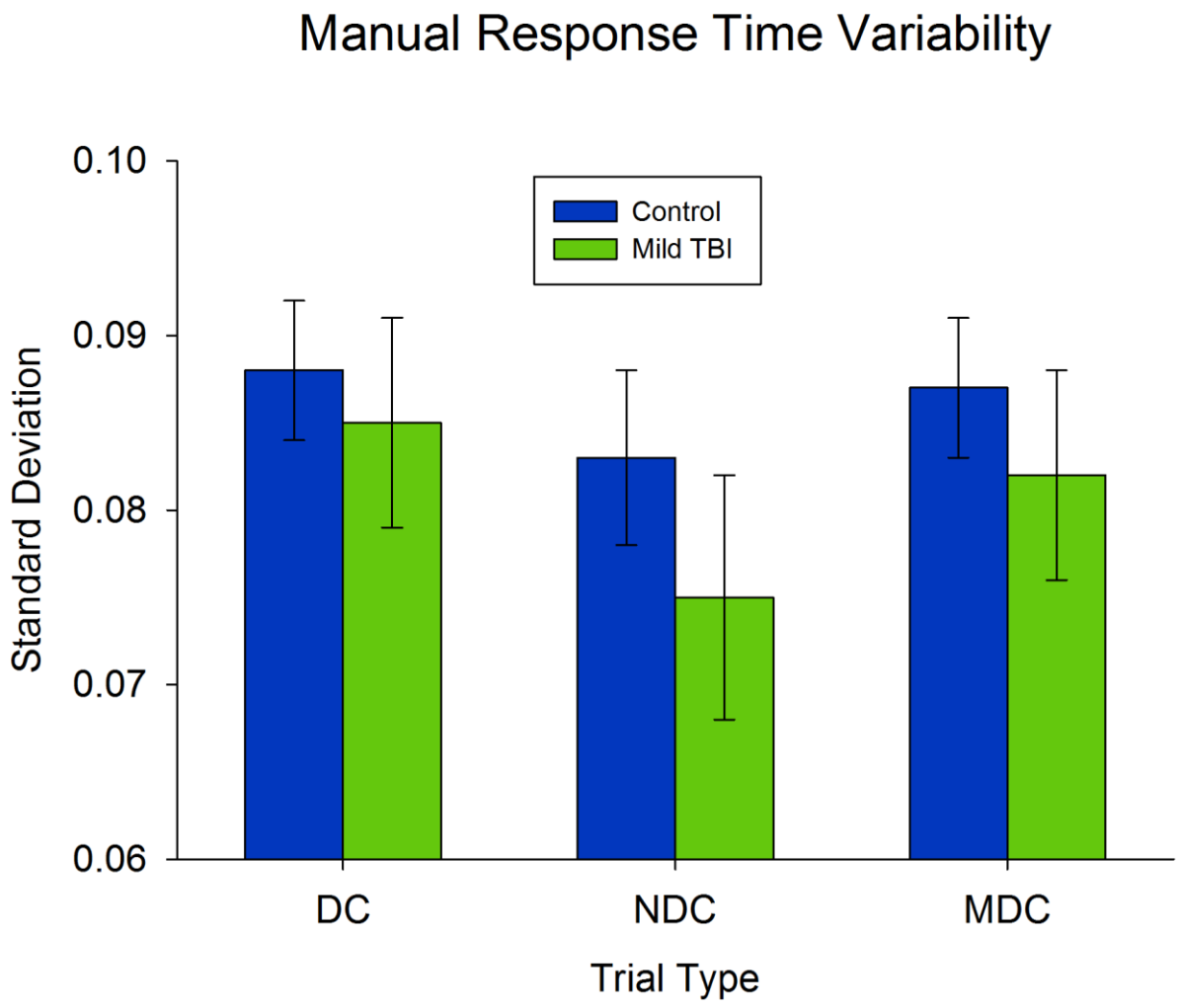


Figure 3: Baseline Pupil Diameter

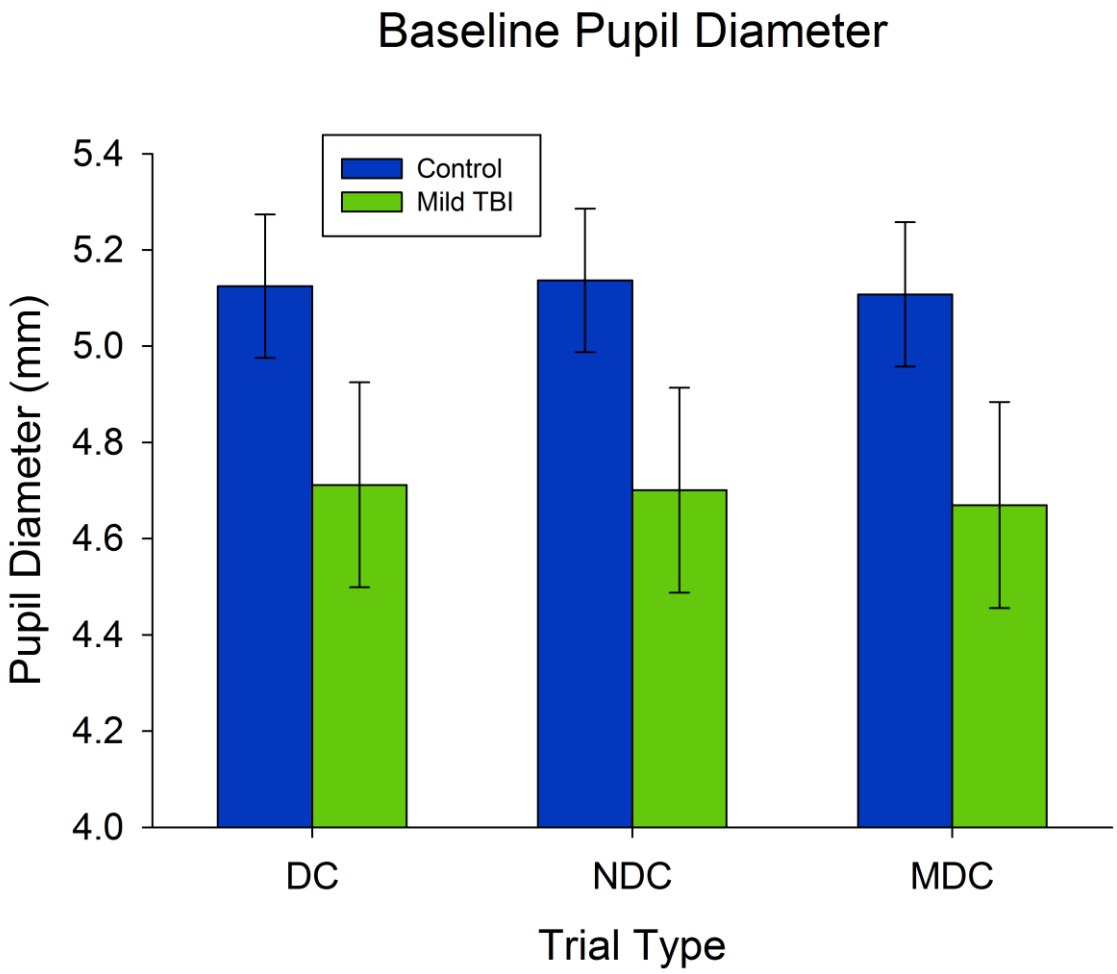


Figure 4: Baseline Pupil Diameter Variability

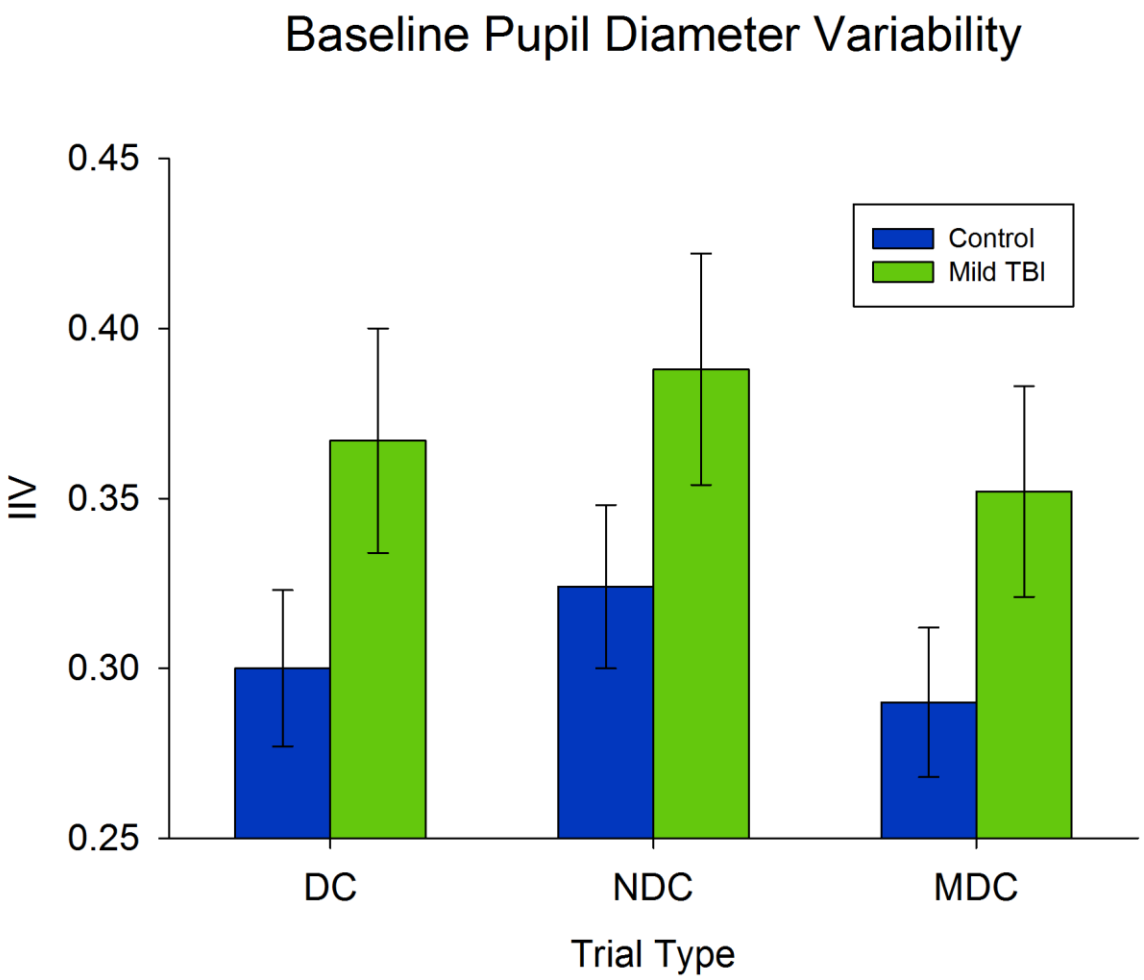


Figure 5: Change in Baseline Pupil Diameter over Trials. *Note: Dotted lines indicate the first trial of a new block.*

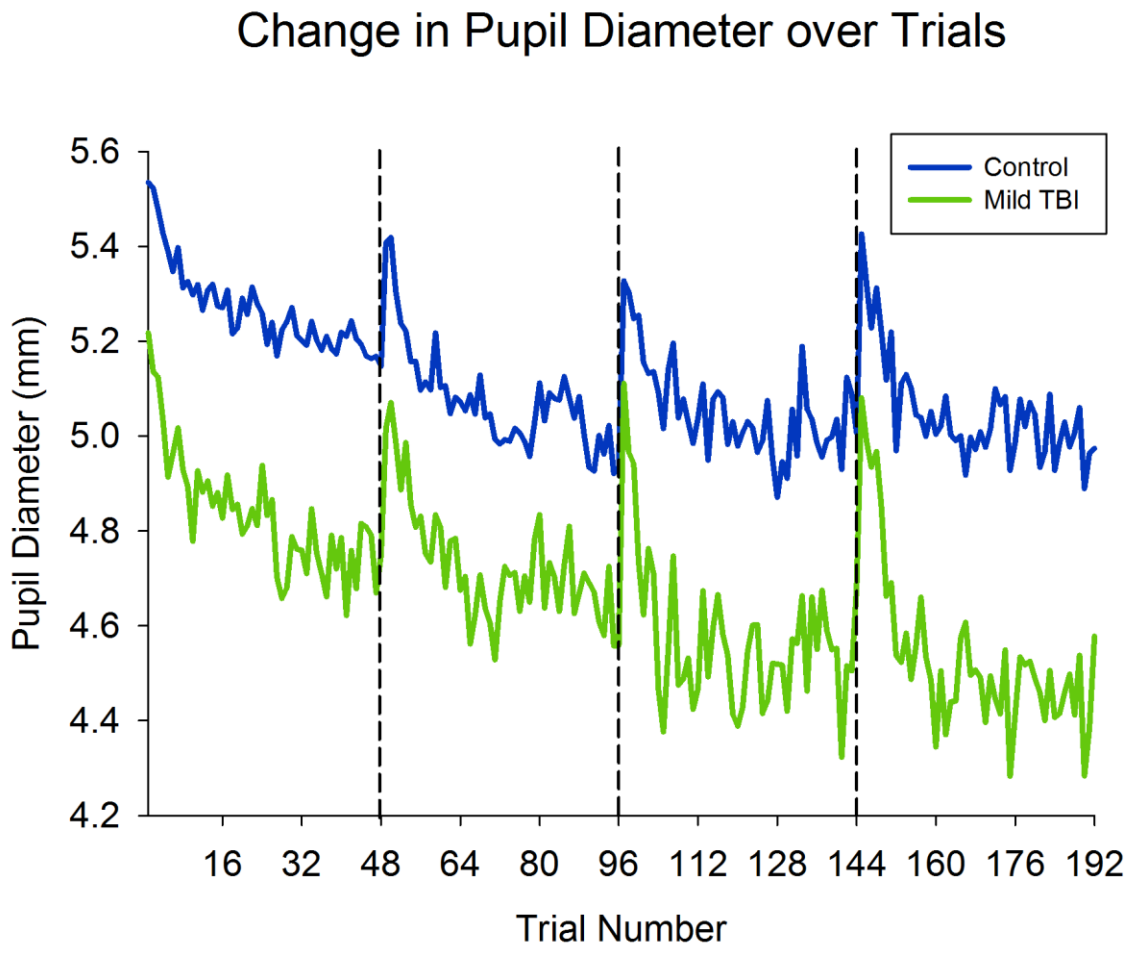


Figure 6: Percent Change in Pupil Diameter Relative to Baseline

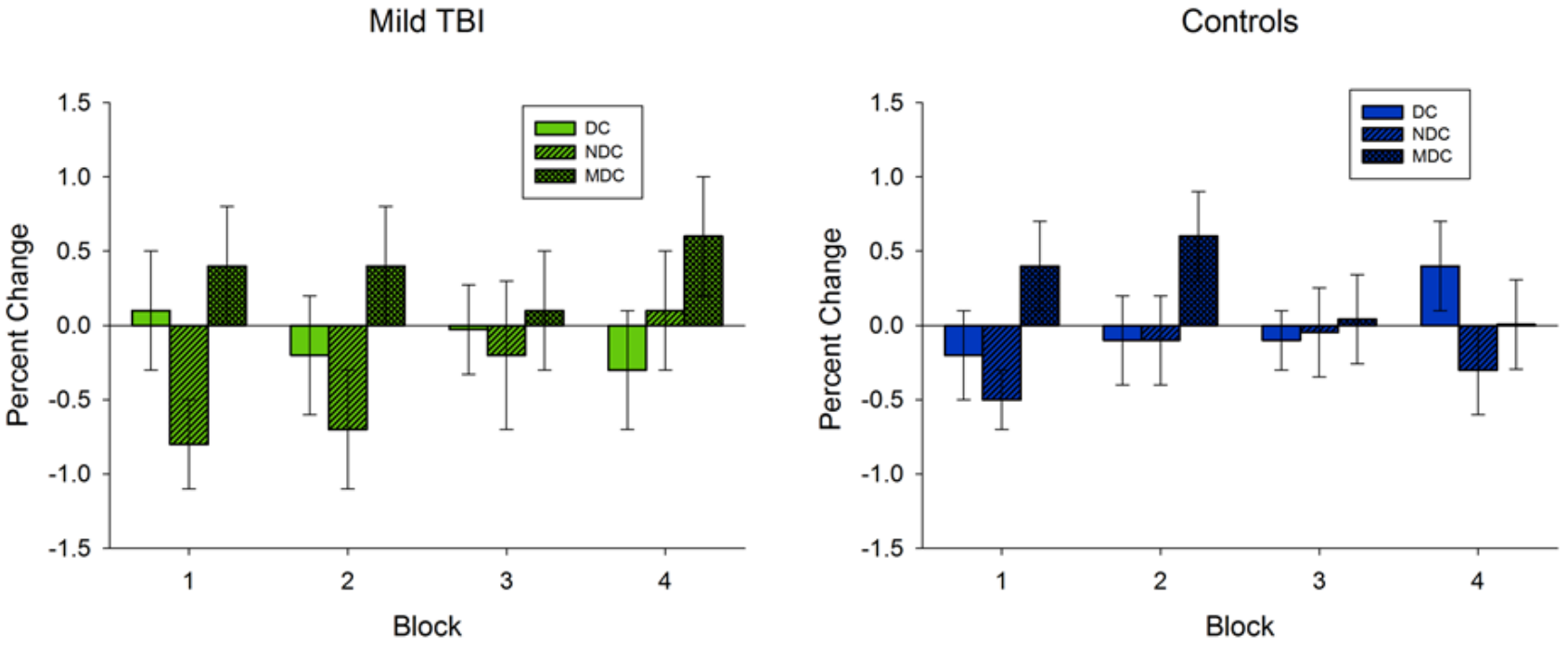


Figure 7: Pupillary Waveforms for Each Trial Type. *Note: Puple dotted lines represent the onset of cues; red dotted lines represent the onset of targets.*

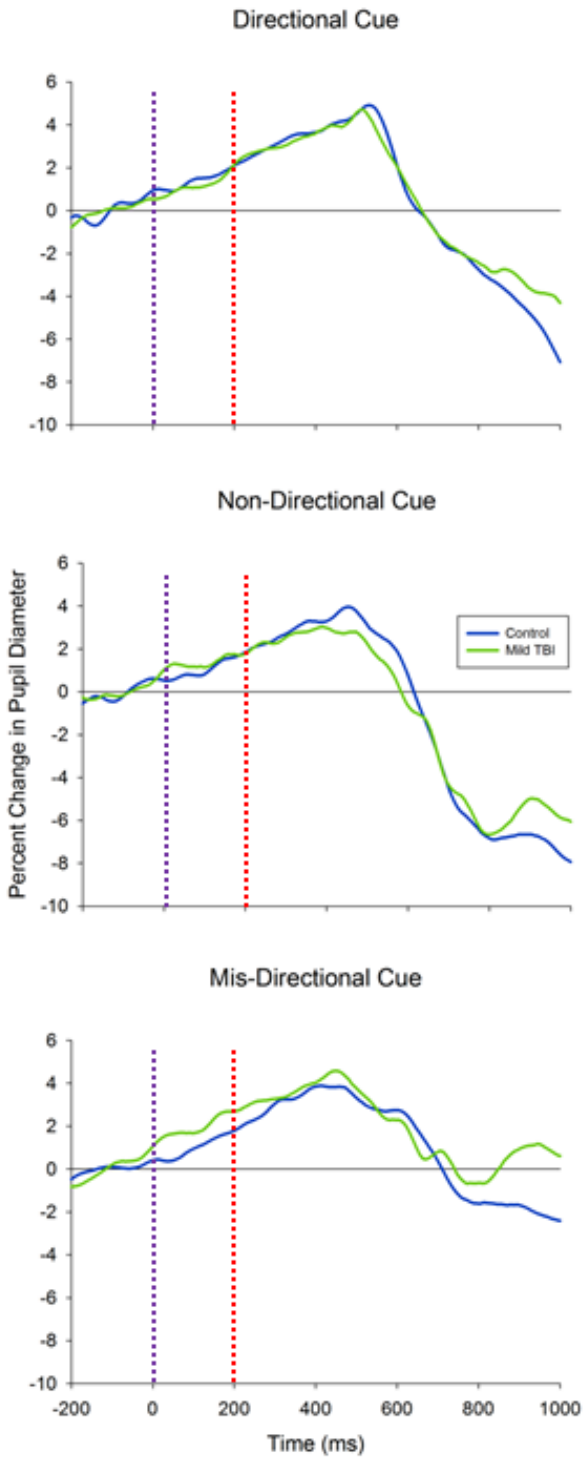
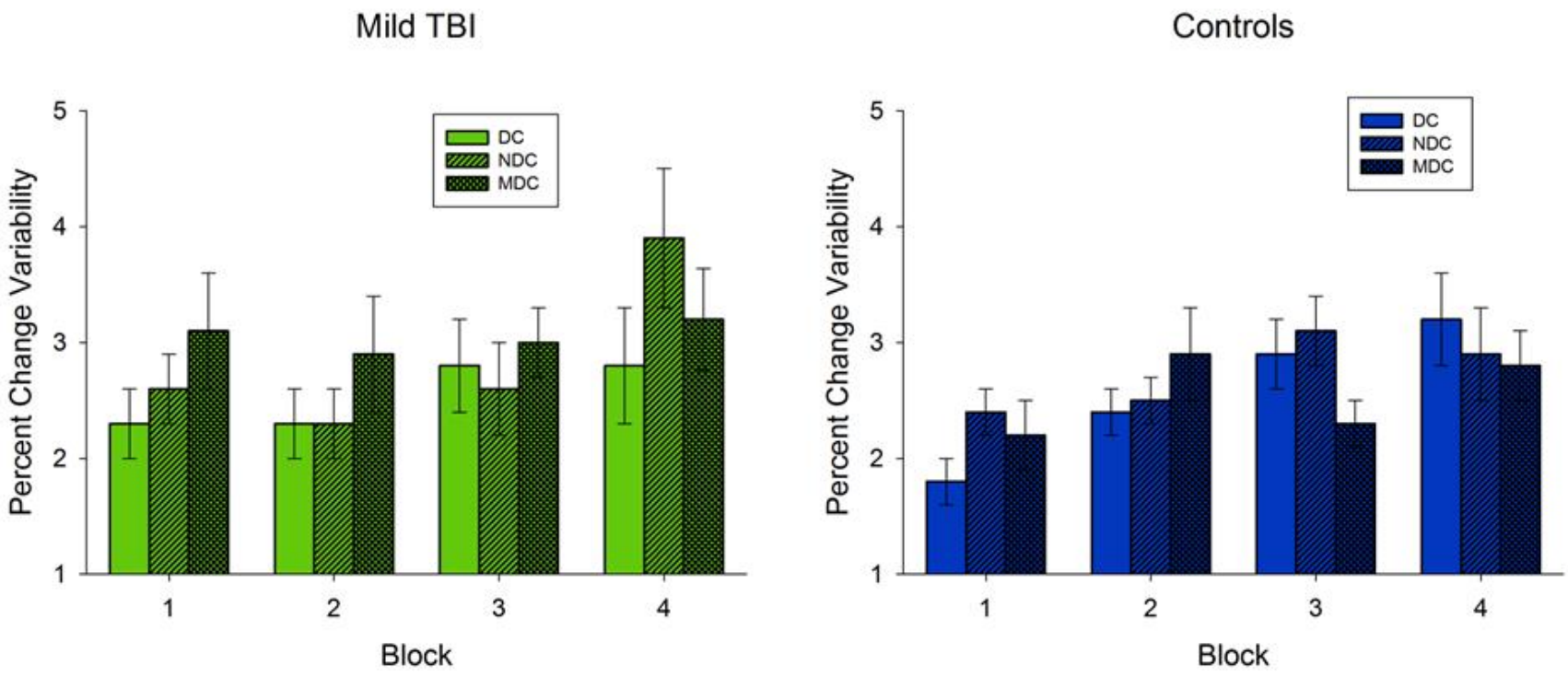


Figure 8: Variability of Percent Change in Pupil Diameter Relative to Baseline



Tables

Table 1. Participant characteristics

		Control N=51 M (SD)	Mild TBI N=25 M (SD)	t value	p value
Gender†					
	Male	24	11	0.063	0.802
	Female	27	14		
Age (years)		33.31 (11.52)	35.32 (12.97)	-0.684	0.496
Ethnicity†					
	Caucasian	28	17		
	Hispanic	3	1		
	Asian	4	1	1.348	0.853
	African American	14	5		
	Other	2	1		
Education (years)		16.35 (2.60)	16.08 (2.12)	0.456	0.65
Number of TBIs†					
	1	0	18		
	2 or more	0	7		
Years since Injury		--	13.8 (13.66)		
Premorbid IQ		108.82 (11.44)	110.84 (9.20)	-0.767	0.445
NSI Score		7.88 (8.77)	12.96 (10.43)	-2.227	0.029*

Notes: * denotes statistical significance, $p<.05$; † denotes values represent frequencies and test statistic is χ^2

Table 2. Descriptive data for block effect in cue-locked pupil diameter variability

	Mean	SE	p-value
Block 1	.024	.002	
vs. Block 2			.226
vs. Block 3			.050*
vs. Block 4			.001*
Block 2	.026	.002	
vs. Block 3			.224
vs. Block 4			.011*
Block 3	.028	.002	
vs. Block 4			.081
Block 4	.031	.002	

Note: * denotes significance at alpha=.05

Table 3. Correlations between pupillary and behavioral outcomes on the BEAM in mild TBI

	Baseline Pupil Diameter	Baseline Pupil Diameter IIV	Baseline Slope	Cue-Locked Pupil Diameter			Cue-Locked Pupil Diameter IIV		
				DC	NDC	MDC	DC	NDC	MDC
Response Time									
DC	-0.209	0.079	0.260	-0.420*	-0.288	-0.300	-0.133	0.056	0.375†
NDC	-0.208	0.035	0.353†	-0.481*	-0.345†	-0.363†	-0.137	0.007	0.372†
MDC	-0.142	0.089	0.212	-0.363†	-0.253	-0.243	-0.147	0.018	0.330
Response Time IIV									
DC	-0.188	0.009	0.369†	-0.578**	-0.38†	-0.521**	-0.141	0.076	0.252
NDC	-0.264	-0.084	0.189	-0.592**	-0.539**	-0.521**	-0.227	-0.147	0.208
MDC	-0.057	-0.230	0.337	-0.439*	-0.374†	-0.489*	-0.194	-0.103	-0.042

Notes. * p<.05; ** p<.01, **p<.001, † p<.09; n=25

Table 4. Correlations between pupillary and behavioral outcomes on the BEAM in uninjured controls

	Baseline Pupil Diameter	Baseline Pupil Diameter IIV	Baseline Slope	Cue-Locked Pupil Diameter			Cue-Locked Pupil Diameter IIV		
				DC	NDC	MDC	DC	NDC	MDC
Response Time									
DC	0.099	-0.068	0.032	-0.265†	-0.108	-0.274†	-0.069	-0.062	-0.03
NDC	0.144	-0.029	0.052	-0.246†	-0.116	-0.292*	-0.031	-0.093	-0.001
MDC	0.088	-0.044	0.070	-0.205	-0.066	-0.201	-0.070	-0.100	0.048
Response Time IIV									
DC	0.177	-0.003	0.238†	-0.145	0.115	-0.128	0.154	0.092	0.063
NDC	0.110	0.140	0.004	-0.142	0.059	-0.168	0.151	0.144	0.001
MDC	0.004	0.134	0.099	-0.108	0.094	-0.180	0.359**	0.221	0.224

Notes. * p<.05; ** p<.01, **p<.001, † p<.09; n=51

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